Universität Basel

Research Project

Deciphering speed and robustness: C-di-GMP signaling in bacterial surface colonization and virulence.

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Project title Deciphering speed and robustness: C-di-GMP signaling in bacterial surface colonization and virulence.
Principal Investigator(s) Jenal, Urs ;
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Departement Biozentrum / Growth & Development
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Department
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When pathogenic or non-pathogenic bacteria colonize surfaces or host tissues they rapidly change their behavior and develop surface-based motility, express virulence traits and eventually mature into multicellular communities, called biofilms. Biofilms are difficult to eradicate in the host as they feature increased drug resistance and persister rates and provide tolerance against phagocytic clearance. In the past years, c-di-GMP was identified as a key regulator of bacterial surface colonization and biofilm formation. This provides an opportunity for pharmacological intervention with clinically problematic forms of bacterial growth. Here we analyze the role of c-di-GMP signaling in the initial steps of surface colonization and biofilm formation in several bacterial model organisms. We address how bacteria perceive mechanical stimuli and how such cues are transmitted into rapid and robust changes in cell behavior including surface-based motility, attachment and expression of virulence factors.

In the first part we dissect the role of the rotary flagellum as mechanosensory device. We use ***Caulobacter crescentus*** to determine the molecular basis of mechanosensation, by focusing on the flagellar motor and a recently identified diguanylate cyclase involved in surface sensing. We also examine a c-di-GMP-dependent positive feedback loop in mechanotransduction consisting of a novel family of CheY proteins, which modulate motor activity upon activation by c-di-GMP. In the second part we dissect the role of c-di-GMP in surface attachment and virulence of the opportunistic pathogen ***Pseudomonas aeruginosa***. We have recently identified a novel c-di-GMP effector protein that is activated upon *P. aeruginosa* surface recognition to direct the assembly and activity of polar Type IV pili (TFP). Using this protein as biosensor for surface interaction we plan to dissect the molecular and cellular mechanisms involved in *P. aeruginosa* surface recognition, in c-di-GMP dependent TFP activity and in the resulting virulence behavior. In the third part, we aim at exploring the mechanism and role of a central molecular switch in ***Escherichia coli*** that provides for robust and stable transitions of c-di-GMP levels as cells enter and exit the surface-based lifestyle. We will dissect the molecular basis for bi-stable expression and activity of a moonlighting enzyme acting as phosphodiesterase and as transcription factor. We will determine the basis for its strong cooperative behavior and how this contributes to cellular robustness. Finally, to appreciate the global role of this central cellular switch, we will define the entire genetic regulon controlled by the switch and elucidate its role in *E. coli* surface growth.

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Keywords c-di-GMP, second messenger, signaling, Caulobacter, Pseudomonas aeruginosa, E. coli, surface adaptation, biofilm, virulence
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